FORM PTO-1390 (REV. 11-2000) U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: CV-0290

U S APPLICATION NO (If known, see 37 CFR 1 5): 09/936421

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/02194	13 March 2000	12 March 1999

TITLE OF INVENTION: Iodine Preparation Composition

APPLICANT(S) FOR DO/EO/US: Dave Parsons; Elizabeth Jacques; Philip Bowler

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information:
    WO 00/54593 (copy)
    IPER
    Letter in response to the first written opinion

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/936421	PCT/EP00/02194	CV-0290

21. [x] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1000.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$710.00**	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$690.00**	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$
Total claims	28 - 20 =	8	x **$18.00**	$ 144.00
Independent claims	1 - 3 =		x **$80.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$
TOTAL OF ABOVE CALCULATIONS =				$1,004.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$
SUBTOTAL =				$
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$
TOTAL NATIONAL FEE =				$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$ 1,004.00
			Amount to be refunded:	$
			charged:	$

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-3869 . A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Stuart E. Krieger
Bristol-Myers Squibb Company
100 Headquarters Park Drive
Skillman, New Jersy 08558

Stuart E. Krieger
SIGNATURE

Stuart E. Krieger
NAME

28,731
REGISTRATION NUMBER

Iodine Preparation Composition

This invention relates to an antimicrobial composition which can be applied to wounds, cuts, abrasions or burns for the prevention or treatment of infections. More particularly the invention relates to a composition capable of providing effective antimicrobial activity while at the same time avoiding wound and skin irritation and retardation of wound healing.

Topical antimicrobial materials and preparations containing them have long been recognised as important parts of antisepsis of intact skin and wounds. Iodine has been recognized as an antimicrobial agent with effectiveness against a wide range of micro-organisms. There are however several barriers to making an effective antimicrobial composition for application to wounds based on iodine. One problem is that iodine tends to react with organic materials found in the wound other than the intended microbial targets. This means that to be effective, iodine needs to be included at high levels such as 0.9% by weight, as described in "Handbook of Wound Dressings" edited by Stephen Thomas, 1994 Journal of Wound Care. . At such levels and with continued use iodine may have undesirable local side effects such as cell toxicity, hypersensitivity reactions, skin staining, and unpleasant odour and systemic adverse effects such as metabolic acidosis and impairment of renal function. For this reason application of iodine is recommended at levels below 1.35g in one week.

A further problem is that iodine has a relatively short shelf life when in aqueous solution meaning either that compositions which include water need to be freshly prepared before each application or again that iodine is included at high levels. These factors limit product form.

In the past these problems with iodine have sought to be addressed by the use of iodophors which act as a release mechanism for iodine. Iodophors are readily dissociable, loose complexes of iodine with polymers or surfactants. Iodophor compositions are not best suited to use on wounds because when applied to a wound, all iodine present in the composition is readily available for reaction and therefore the adverse reactions associated with high levels of iodine are not necessarily avoided.

There thus exists a need for a composition which delivers iodine to a wound at a rate which is high enough to provide effective antisepsis but which is low enough
to avoid the problems of adverse reactions associated with high levels of iodine.

GB-B-2276546 to Diversey relates to improved iodophors which are prepared at the point of use. The composition comprises an iodide source, an oxidant and an acid source, the oxidant becoming active only when the composition is dissolved in an aqueous medium. The composition is said to overcome the stability problems associated with producing teat dip/spray iodine formulations for use in

the control of bovine mastitis. The rate of generation of iodine needed for these topical formulations for use on intact skin far exceeds that tolerable to a wound. In these compositions such high levels of iodine are generated that a hydrotrope must be included to prevent the iodine from crystallising. In addition, iodine has a complex chemistry in aqueous solutions and exists in a number of equilibria. At high iodine concentrations in the presence of iodide there is a strong tendency for the tri-iodide ion to form. We believe that this ion has very little antimicrobial activity but can still be absorbed with the risk of systemic toxicity.

We have found that it is possible to prepare a composition which is capable of generating iodine at a rate and level that makes it suitable for use in wounds. This is achieved by separating certain of the ingredients and controlling the kinetics of the generation of iodine through the manipulation of pH.

Accordingly the present invention provides an iodine preparation composition suitable for use on wounds comprising an iodide source, an oxidant and a buffer characterised in that the oxidant is held separately from the iodide until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable and efficacious rate.

The invention allows the preparation of compositions generating a low but effective iodine level for example up to about 2000µg per g of composition per

hour, preferably in the range of 5μg per g of composition per hour to 1500μg per g of composition per hour, more preferably in the range 50μg per g of composition per hour to 1000μg per g of composition per hour so that the amount of free iodine available for antisepsis at any time is at least 0.001%.

The compositions of the invention are preferably formulated to generate the above levels of iodine over a period of about 3 days.

The pH of the composition of the invention is generally below 5.8. We have found that if the pH is greater than about 6, the rate of production of iodine by reaction of the oxidising agent with iodide ions is too low to balance any losses of iodine by reaction with the organic matter. We have found that it is generally desired that the pH of the compositions is not below about 4.5 as otherwise there is a danger that the rate of oxidation of the iodide ions will be too fast with the result that the composition could become toxic.

The desired pH of the compositions may be achieved by incorporating buffering agents therein. Examples of buffering agents which may be included are citric acid/disodium hydrogen phosphate, citric acid/sodium citrate, acetic acid/sodium acetate. The buffering agent may conveniently be present in an amount of about 2% to 10%, preferably about 4% to 6% by weight and particularly about 5% by weight so as to provide an isotonic composition.

The amount of oxidant in the composition is tailored to provide a stoichiometric match with iodide. Preferably the oxidant is iodate and is provided in a molar ratio of 1:5 with iodide. In this way the iodide present in the composition fully reacts with all the oxidant. To provide the levels and rate of production of iodine in the range described above it is desirable to include up to 2% by weight of iodide, preferably, from 0.2 % to 2 % by weight of iodide. Iodide and iodate are preferably present as sodium salts although other usual counter ions may be used.

Convenient forms of administration of the composition include aqueous gels, films, creams, tablets and capsules.

The following examples are illustrative of the present invention.

Example 1.

Gel A	Weight g
Hydroxyethyl cellulose	30.00
Propylene Glycol	150.00
Na_2HPO_4	35.61
Citric Acid	21.01
Potassium Iodate	1.124
Water	762.256

Gel B	Weight in g

Hydroxyethyl cellulose	30.0
Propylene Glycol	150.0
Potassium Iodide	4.36
Water	815.64

Gel A was made by dissolving the buffer salt in a water/propylene glycol mix and then adding the iodate. When the solution is clear the hydroxyethyl cellulose is added and mixed until gelation is complete. Gel B was made by dissolving iodide in a water/propylene glycol mix. Hydroxyethyl cellulose was added to this mixture and mixed until gelation was complete.

The gels were packaged in separate syringes which were bound together with their nozzles fitted into a Y-shaped connecter. The contents were sterilised by autoclaving at 121 C for 15 minutes. Simultaneous depression of the plungers allows the gels to be co-extruded and allows the gels to react while being dispensed into a wound. The co-extrusion of the gels results in a product producing approximately 100μg per g of composition per hour at a pH of about 5.4. The composition generated a greater than 5 log kill of *S. aureous* (NCIMB 9518) which is regarded as being an acceptable level of antimicrobial activity.

Example 2

Film A g

Hydroxypropylcellulose	16
Propylene Glycol	4
Potassium Iodate	0.1124
Sodium phosphate	1.7805
Citric acid	1.0505
Water	77.0566

Film B

Hydroxypropylcellulose	16
Propylene Glycol	4
Potassium Iodide	0.436
Water	79.564

The films are produced by knife over roller coating of aqueous solution onto an inert carrier, followed by drying at a temperature not exceeding 100 C and sterilised by gamma irradiation.

The films may be cut into rectangles and added to a wound whereupon they dissolve in the wound fluid and reaction takes place.

CLAIMS:

1. An iodine preparation composition suitable for use on wounds comprising an iodine source, and oxidant and a buffer characterised in that the iodine is held separately from the oxidant until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable dose and rate.

2. An iodine preparation composition as claimed in claim 1 characterised in that the composition is capable of generating from 5µg of iodine per g of composition per hour to 1500µg of iodine per g of composition per hour, preferably 100µg of iodine per g of composition per hour.

3. An iodine composition as claimed in claim 2 formulated to generate the said levels of iodine over a period of three days.

4. An iodine composition according to any preceding claim wherein the pH of the composition is maintained between 5.4 and 5.8.

5. An iodine composition according to any preceding claim which includes from 0.2% to 2% by weight of iodine.

6. The use of an iodine preparation composition according to any preceding claim for the manufacture of a medicament for use on wounds.

7. Use of an iodine preparation composition according to any preceding claim for the treatment of wounds.

8. Use according to claim 6 or 7 for the treatment of sepsis in wounds.

Attorney Docket No. CV-0290

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for which a patent is sought on the invention **IODINE PREPARATION COMPOSITION** the specification of which

[ ] is attached hereto
[x] was filed on September 12, 2001 as Application Serial No. 09/936,421

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, ∋1.56(a).

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business to the Patent and Trademark Office connected therewith: Theodore R. Furman, Reg. No. 30,942. Address all correspondence to Theodore R. Furman, Jr. c/o Bristol-Myers Squibb Company, 100 Headquarters Park Drive, Skillman, New Jersey 08558. Telephone (908) 904-2372.

I hereby claim foreign priority benefits under Title 35, United States Code, ∋119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIORITY FOREIGN APPLICATION(S)

Number	Country	Filed (day/month/year)	Priority Claimed (Yes or No)
9905663.2	Great Britain	12 March 1999	Yes

I hereby claim the benefit under Title 35, United States Code, ∋120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, ∋112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, ∋1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application S.N.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of sole or first inventor Dave Parsons

Inventor's signature Dave Parsons Date 19th November 2001

Resident (Town and State) HESWALL, WIRRAL.

Citizenship British

Post Office Address 6 Briar Drive GBX

Heswell, Wirral L60 5RN, United Kingdom

2-00

Full name of second inventor Elizabeth Jacques

Inventor's signature Elizabeth Jacques. Date 19th November 2001

Resident (Town and State) CHESTER, CHESHIRE

Citizenship British

Post Office Address 9 Cedar Grove

Hoole, Chester CH2 3LQ, United Kingdom GBX

3-00

Full name of third inventor Philip Bowler

Inventor's signature Ph Bowler Date 20-11-01.

Resident (Town and State) WARRINGTON, CHESHIRE

Citizenship British

Post Office Address 8 Woodbridge Close, Appleton, Warrington,

Cheshire WA4 5RD, United Kingdom GBX